REMARKS

Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26, 30 and 61-71 are pending in the present application. Claims 8, 9, 13-16, 20-22 and 27-29 have been withdrawn from further consideration as directed to a non-elected invention. Claims 3-4, 17, 23-26 and 31-60 have been cancelled previously, and claims 5, 6, 7, 11, 12, 62-64, 66 and 67 are cancelled herein. Claims 1, 30, 61, 68, 69 and 71 are amended herein and new claims 72-78 have been added. Therefore, claims 1, 2, 10, 18, 19, 30, 61, 65 and 68-78 are presently under consideration. The cancellation of claims 5, 6, 7, 11, 12, 62-64, 66 and 67 and the amendment of claims 1, 30, 61, 68, 69 and 71 herein have been effected so as to accelerate prosecution of the instant application. Applicants may pursue claims to additional subject matter in one or more divisional applications. A clean listing of the pending claims begins on page 25 of this Response. Reconsideration of all pending claims is respectfully requested in view of the amendments made and the following remarks.

The Examiner has provisionally rejected claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 on the ground of nonstatutory obvious-type double patenting as being unpatenable over claims 1-2, 4-5, 22, 23, and 25-35 of copending Application No. 12/399,610 (the '610 application). Applicants aver that the present application has been amended herein to claim systemic inflammatory (*i.e.,* nonfibrotic) conditions, such that the claims of the '610 application and the current claims are patentably distinct. Thus, Applicants respectfully request the provisional double patenting rejection be withdrawn.

The Examiner has rejected claims 61, 68-69 and 71 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter that Applicants regard as the invention. Claims 68 and 69 have been amended to address the lack of antecedent basis for phrases contained in those claims. Additionally, the Examiner states that claims 61 and 71 are ambiguous for recitation of "follistatin 288 or follistatin 315." Applicants have amended claims 61 and 71 herein to recite "wherein follistatin is either follistatin isoform 288 or follistatin isoform 315." Support for this amendment can be found at page 5, lines 21-29 in the application as filed. In view of these amendments, Applicants respectfully request that the rejection of claims 61, 68, 69 and 71 under 35 U.S.C. §112, second paragraph be withdrawn.

The Examiner has rejected claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 under 35 U.S.C. §102(b) as being allegedly anticipated by WO 03/006006057 (hereinafter "the '057 publication"). Applicants have made amendments to claim 1 herein so that claim 1 is now drawn to systemic inflammatory conditions (*i.e.,* nonfibrotic inflammatory conditions); that is, claim 1 now recites, "A method of downregulating the inflammatory response in a mammal, ...wherein the inflammatory response is a systemic inflammatory response", and claim 2 has been similarly amended. Also, new claims 72-78 recite specific nonfibrotic inflammatory conditions. Applicants submit, therefore, that because the '057 publication is directed specifically to treatment of fibrotic disorders, the '057 publication is is no longer apposite to the claims as amended, and respectfully request that the rejection of the claims under 35 U.S.C. §102(b) as allegedly being anticipated by WO 03/006006057 be withdrawn.

The Examiner has rejected Claims 1, 2, 5-7,10-12, 18, 19, 30 and 61-71 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent Publication 2002/0192216 (hereinafter 'the '216 publication) as evidenced by van Eyll et al. The '216 publication discloses that follistatin is an inhibitor of the Hedgehog signaling pathway, and the '216 publication does recite "septic shock" as one of many diseases treatable by inhibiting the Hedgehog signaling pathway.

As Applicants have argued previously, the '216 publication discloses that follistatin is an inhibitor of an intracellular signaling pathway, but fails to provide an enabling disclosure regarding the use of follistatin to treat any therapeutic indication. Again, Applicants note that the '216 publication was abandoned after a lengthy prosecution during which the Examiner in the case repeatedly rejected the application ('216 publication) as failing to provide a written description. The Examiner noted that the Applicant of the '216 publication disclosed only limited species of antigens recognized by antagonistic antibodies, namely shh, HIP, WIF1 and Dv1, and concluded that the Applicant of the '216 publication was not in possession generally of antagonistic antibodies to the recited signaling pathways or targets of the signaling pathways. No examples or evidence was presented in the '216 publication relating to the efficacy of follistatin to treat any disease, disorder or condition.

The Examiner further has cited *In re Hafner*, 410 F.2d 1403 (CCPA 1969) for the premise that the standards for enablement under 35 U.S.C. §112 for patentability and enablement

under 35 U.S.C. §102 for an anticipatory disclosure are different. Applicants concur with this premise. However, "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997).* Moreover, it is settled law that "[t]he disclosure of an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation." *Elan Pharm., Inc., v. Mayo Found., 346 F.3d 1051, 1054 (Fed. Cir. 2003).* Applicants contend that the '216 publication is not enabling, at least as far as follistatin is concerned; accordingly, the '216 publication does not anticipate the subject matter of the claimed invention.

The Examiner has argued that *In re Donohue, 766 F.2d 531 (Fed. Cir. 1985)* stands for the premise that a reference contains an enabling disclosure 'if the public was in possession of the claimed invention before the date of invention, and that such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention.' Applicants do not dispute the Examiner's characterization of *In re Donohue*; however, Applicants do dispute whether the public would have been in possession of any therapeutic treatment given the disclosure in the '216 publication. Specifically, the '216 publication teaches administration of an inhibitor of the Hedgehog signaling pathway to treat:

> ...adult respiratory distress syndrome; chronic obstructive airway disorders/chronic obstructive pulmonary disease including asthma, emphysema and chronic bronchitis; atelectasis; occupational lung disease including silicosis; hypersensitivity diseases of the lung including hypersensitivity pneomonitis; idiopathic interstitial lung diseases including idiopathic pulmonary fibrosis, usual interstitial pneumonia, desquamative interstitial pneumonia and acute interstitial pneumonia; and pleural fibrosis.... The present invention is also useful in treating immune disorders such as autoimmune diseases or graft rejection such as allograft rejection.
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> Examples of disorders that may be treated include a group commonly called autoimmune diseases. The spectrum of autoimmune disorders ranges from organ specific diseases (such as thyroiditis, insulitis, multiple sclerosis, iridocyclitis, uveitis, orchitis, hepatitis, Addison's disease, myasthenia gravis) to systemic illnesses such as rheumatoid arthritis or lupus erythematosus. Other disorders include immune hyperreactivity, such as allergic reactions.
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> In more detail: Organ-specific autoimmune diseases include multiple sclerosis, insulin dependent diabetes mellitus, several forms of anemia (aplastic, hemolytic), autoimmune hepatitis, thyroiditis, insulitis, iridocyclitis, skleritis, uveitis, orchitis,

myasthenia gravis, idiopathic thrombocytopenic purpura, inflammatory bowel diseases (Crohn's disease, ulcerative colitis).

Systemic autoimmune diseases include: rheumatoid arthritis, juvenile arthritis, scleroderma and systemic sclerosis, sjogren's syndrom, undifferentiated connective tissue syndrome, antiphospholipid syndrome, different forms of vasculitis (polyarteritis nodosa, allergic granulomatosis and angiitis, Wegner's granulomatosis, Kawasaki disease, hypersensitivity vasculitis, Henoch-Schoenlein purpura, Behcet's Syndrome, Takayasu arteritis, Giant cell arteritis, Thrombangiitis obliterans), lupus erythematosus, polymyalgia rheumatica, essentiell (mixed) cryoglobulinemia, Psoriasis vulgaris and psoriatic arthritis, diffus fasciitis with or without eosinophilia, polymyositis and other idiopathic inflammatory myopathies, relapsing panniculitis, relapsing polychondritis, lymphomatoid granulomatosis, erythema nodosum, ankylosing spondylitis, Reiter's syndrome, different forms of inflammatory dermatitis.

A more extensive list of disorders includes: unwanted immune reactions and inflammation including arthritis, including rheumatoid arthritis, inflammation associated with hypersensitivity, allergic reactions, asthma, systemic lupus erythematosus, collagen diseases and other autoimmune diseases, inflammation associated with atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, vascular inflammatory disorders, respiratory distress syndrome or other cardiopulmonary diseases, inflammation associated with peptic ulcer, ulcerative colitis and other diseases of the gastrointestinal tract, hepatic fibrosis, liver cirrhosis or other hepatic diseases, thyroiditis or other glandular diseases, glomerulonephritis or other renal and urologic diseases, otitis or other oto-rhino-laryngological diseases, dermatitis or other dermal diseases, periodontal diseases or other dental diseases, orchitis or epididimo-orchitis, infertility, orchidal trauma or other immune-related testicular diseases, placental dysfunction, placental insufficiency, habitual abortion, eclampsia, pre-eclampsia and other immune and/or inflammatory-related gynaecological diseases, posterior uveitis, intermediate uveitis, anterior uveitis, conjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, intraocular inflammation, e.g. retinitis or cystoid macular oedema, sympathetic ophthalmia, scleritis, retinitis pigmentosa, immune and inflammatory components of degenerative fondus disease, inflammatory components of ocular trauma, ocular inflammation caused by infection, proliferative vitreo-retinopathies, acute ischaemic optic neuropathy, excessive scarring, e.g. following glaucoma filtration operation, immune and/or inflammation reaction against ocular implants and other immune and inflammatory-related ophthalmic diseases, inflammation associated with autoimmune diseases or conditions or disorders where, both in the central nervous system (CNS) or in any other organ, immune and/or inflammation suppression would be beneficial, Parkinson's disease, complication and/or side effects from treatment of Parkinson's disease, AIDS-related dementia complex HIV-related encephalopathy, Devic's disease, Sydenham chorea, Alzheimer's disease and other degenerative diseases, conditions or disorders of the CNS, inflammatory components of stokes, post-polio syndrome, immune and inflammatory components

> of psychiatric disorders, myelitis, encephalitis, subacute sclerosing pan-encephalitis, encephalomyelitis, acute neuropathy, subacute neuropathy, chronic neuropathy, Guillaim-Barre syndrome, Sydenham chora, myasthenia gravis, pseudo-tumour cerebri, Down's Syndrome, Huntington's disease, amyotrophic lateral sclerosis, inflammatory components of CNS compression or CNS trauma or infections of the CNS, inflammatory components of muscular atrophies and dystrophies, and immune and inflammatory related diseases, conditions or disorders of the central and peripheral nervous systems, post-traumatic inflammation, septic shock, infectious diseases, inflammatory complications or side effects of surgery or organ, inflammatory and/or immune complications and side effects of gene therapy, e.g. due to infection with a viral carrier, or inflammation associated with AIDS, to suppress or inhibit a humoral and/or cellular immune response, to treat or ameliorate monocyte or leukocyte proliferative diseases, e.g. leukaemia, by reducing the amount of monocytes or lymphocytes, for the prevention and/or treatment of graft rejection in cases of transplantation of natural or artificial cells, tissue and organs such as cornea, bone marrow, organs, lenses, pacemakers, natural or artificial skin tissue.
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> The present invention is also useful in cancer therapy, particularly in diseases involving the conversion of epithelial cells to cancer. The present invention is especially useful in relation to adenocarcinomas such as: small cell lung cancer, and cancer of the kidney, uterus, prostrate, bladder, ovary, colon and breast.

'216 publication at ¶¶149-155.

Applicants contend that the '216 publication tosses out the mere germ of an idea relating to the treatment of a panoply of diseases, and that one skilled in the art would have been hard pressed to identify follistatin specifically as one of the many disclosed inhibitors of the Hedgehog signaling pathway as a therapeutic agent without undue experimentation. Further, one skilled in the art would have had to perform an enormous amount of experimentation to arrive at systemic inflammatory conditions—or any other specific therapeutic indication for that matter—as a likely therapeutic indication given the laundry list of diseases, disorders, conditions, etc., that are disclosed in the '216 publication. Thus, Applicants respectfully submit that one skilled in the art would have had to perform an undue amount of experimentation to arrive at the working combination of follistatin as a therapeutic agent and systemic inflammatory conditions as a therapeutic indication out of the colossal number of permutations and combinations of therapeutic agents and therapeutic indications possible upon reading the '216 reference. Indeed, Dr. David de Kretser so states at ¶ 8 of the Declaration of David Morritz de Kretser ("de Kretser Declaration") submitted herewith. In addition, Dr. de Kretser concludes that there is a high likelihood that a therapeutic response may not be achieved even with a vast amount of

experimentation. Moreover, as Dr. de Kretser states in his Declaration at ¶¶4-6, a review of the published literature does not support the information disclosed in the specification of the '216 publication. First, several studies indicate that inhibition of hedgehog signaling actually promotes inflammation, particularly in the gut (discussed in the de Kretser Declaration at ¶4). Second, in animal models of lung disease, hedgehog signaling appears to be upregulated in fibrotic processes, but not in nonfibrotic inflammatory processes (discussed in the de Kretser Declaration at ¶5). Further, the complexity of the hedgehog signaling pathway and the regulation of activins A and B in different systems leads to unpredictability of the effect of activin or follistatin on Shh signaling (discussed in the de Kretser Declaration at ¶6). Dr. de Kretser concludes at ¶7 that the disclosure of the '216 publication—drawn to inhibiting a hedgehog signaling pathway to treat a host of disparate and complex human diseases—is overly simplistic and not supported by studies reported in the literature.

As for van Eyll, et al. (cited by the Examiner), the authors describe Shh-dependent differentiation of intestinal tissue from embryonic pancreatic explants from mice and disclose that Shh signaling can be inhibited by follistatin, but this reference does not provide any evidence that inhibition of Shh or the Hedgehog signaling pathway is effective in treating inflammation or any other of the therapeutic indications listed in the '216 publication.

Therefore, Applicants contend that the '216 reference is not an enabling disclosure and request that the rejection of the claims under 35 U.S.C. §102(b) as allegedly being anticipated by the '216 publication, as evidenced by van Eyll et al., be withdrawn.

The Examiner has rejected claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication 2003/0162715 (hereinafter "the '715 publication"). The '715 publication allegedly discloses follistatin-like-3 protein to treat disease, and mentions sepsis and septic shock as one therapeutic indication treatable by administration of follistatin-like-3 protein. Although the Examiner agreed with Applicants that follistatin-3 is different from follistatin, the Examiner states that those of skill in the art would have had reason to use the follistatin of the instant application as a substitute for the treatment taught in the '715 publication because, like follistatin-3 taught in the '715 publication, follistatins are activin antagonists. The Examiner argues further that substituting a known element for another to yield a known result is obvious (citing *KSR*, 550 U.S. 416, 421 (2007)).

To begin with, Applicants disagree that follistatin-3 (also known as follistatin related-gene or FLRG) are substitutions for one another. Even the '715 reference teaches that, "we demonstrate that FLRG is a functional activin-binding protein which, like follistatin, binds both activin A and activin B... [h]owever, we demonstrate differential expression in tissues and regulation of follistatin and FLRG expression in cultured keratinocytes... [o]ur results indicate differences in the *in vivo* regulation and functions of FLRG and follistatin proteins" (the '715 publication at ¶549). Moreover, as stated in the de Kretser Declaration at ¶10, it is known in the art that follistatin-3 and follistatin are encoded by separate genes and, although they do show some homology, each is a unique protein with distinct roles as demonstrated when the gene for each protein is knocked out. As described in the de Kretser Declaration at ¶10, Matzuk, et al. report that knock-out of the follistatin gene results in the death of all offspring within a few hours after birth. In contrast, disruption of the follistatin-3 gene in mice reported by Mukherjee, et al. resulted in mice surviving to adulthood.

In addition, as stated in the de Kretser Declaration at ¶11, although the two proteins have follistatin domains with some homology, follistatin-3 and follistatin share only 61.5% amino acid sequence similarity and 43.25% identity. Importantly, follistatin has a lysine-rich heparin binding sequence in the follistatin domain 1, which enables follistatin to bind to heparin sulfate proteoglycans on cell surfaces, targeting any follistatin-bound activin to a lysosomal degradation pathway. Follistatin-3 has no such site and cannot initiate the degradation of activin after it is bound. Moreover, it has been demonstrated that follistatin-3 is 50-100 fold less potent in neutralizing the effects of endogenously produced activin production than follistatin, whereas follistatin-3 is only 2.4 fold less potent than follistatin in neutralizing the effects of exogenously added activin A. Dr. de Kretser concludes that given that inflammatory disorders involve the production of endogenous activin at one or more sites, the absence of the heparin binding site in follistatin-3 would render it ineffective as a therapeutic in these settings.

Further, it has been reported in the literature that the effects of follistatin and follistatin-3 on activin A- or BMP2-mediated gene expression are different depending on the target (discussed in the de Kretser Declaration at ¶12); and it has been found in heart failure that follistatin and follistatin-3 have different effects and expression patterns (discussed in the de Kretser Declaration at ¶13). Dr. de Kretser, as one with skill in the art, concludes at ¶14 that the differences between follistatin and follistatin-3 demonstrate that they are not biologically

substitutable one for the other particularly in the context of binding activin. Additionally, Dr. de Kretser at ¶15 states that in his review of the literature, he did not find any reported study demonstrating that follistatin-3 is effective in treating inflammation.

Applicants submit further that the biological and chemical arts are generally accepted to be unpredictable. The Federal Circuit confirmed this in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353 (Fed. Cir. 2008), stating, "[t]o the extent an art is unpredictable, as chemical arts often are, *KSR*'s focus on...'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Id.* at 1359. Applicants argue that this is particularly true when talking about proteins that are as different as follistatin and follistatin-3, as seen in the vastly different results in knock-out models of these proteins.

Additionally, as with the '216 publication, the '715 publication fails to exemplify even one therapeutic indication that can be treated with follistatin-3. Nevertheless, the '715 publication recites that follistatin-3 may be useful in the treatment of:

> Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.
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> Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.
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> Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may also be used to modulate inflammation. For example, follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)....

Examples of hyperproliferative disorders that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects....

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture,

heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis....

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency....

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms.

Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis....

Ocular disorders associated with neovascularization which can be treated with the follistatin-3 polynucleotides and polypeptides of the present invention (including follistatin-3 agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization.

Moreover, disorders and/or states, which can be treated with be treated with the follistatin-3 polynucleotides and polypeptides of the present invention (including follistatin-3 agonist and/or antagonists) include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubcosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by follistatin-3 polynucleotides or polypeptides, as well as antagonists or agonists of follistatin-3, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, follistatin-3 polynucleotides, polypeptides, and/or antagonists of the

invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by follistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia....

[F]ollistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns

resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associted with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Follistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, could be used to promote dermal reestablishment subsequent to dermal loss....

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxyiridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid,

pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

'715 publication at ¶¶392-440.

As argued in relation to the '216 publication, Applicants contend that "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Applicants submit that the '715 publication like the '216 publication simply tosses out the mere germ of an idea to use follistatin-3 to treat a voluminous array of human diseases and disorders without one single example or exemplification of success using follistatin-3 to do so. Thus, Applicants respectfully submit that one skilled in the art would have had to perform an undue amount of experimentation to decipher which, if any, of the therapeutic indications recited in the '715 publication are indeed treatable by follistatin-3--much less follistatin--particularly given the unpredictable nature of the biological arts and the biological differences between follistatin and follistatin-3.

Because follistatin and follistatin-3 are not substitutes for one another, particularly in the context of activin binding, and because the '715 publication like the '216 publication simply tosses out the mere germ of an idea to use follistatin-3 to treat an array of human diseases and disorders, Appliants request that the rejection of the claims under 35 U.S.C. §103(a) as allegedly being obvious in light of the '715 publication be withdrawn.

Claims 1, 2, 5-6, 10-11, 18, 19, 30 and 62-70 stand rejected under 35 U.S.C. §103(a) as unpatentable over WO 8911862 (hereinafter "the '862 publication"). The Examiner alleges that the '862 publication teaches that inhibin is useful in wound healing, autoimmune disease, immunodeficiency disease, transplant rejection and infection, and that those of skill in the art would have had reason to substitute follistatin for the treatment taught in the '862 publication because, like inhibin taught in the '862 publication, follistatin is an activin antagonist. Again, the Examiner argues that substituting a known element for another to yield a known result is obvious (citing *KSR*, at 421); and again, Applicants submit that the biological and chemical arts are generally accepted to be unpredictable (see *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353 (Fed. Cir. 2008), stating, "[t]o the extent an art is unpredictable, as chemical arts often are, *KSR*'s focus on…'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Id.* at 1359).

Applicants argue that this is particularly true when talking about proteins that are as different as follistatin and inhibin. First, as stated in the de Kretser Declaration at ¶17, inhibin and follistatin are different proteins arising from unlinked genes located on separate chromosomes, and comprise very different molecular structures. Inhibin is a member of the transforming growth factor-β (TGF-β) superfamily, and is a dimer consisting of an α-subunit crosslinked to a β-subunit (either βA or βB subunits, which are shared with activin), whereas follistatin is a single-chain polypeptide with three follistatin domains. Second, as described earlier in the context of follistatin-3, knock-out models of follistatin result in a neonatal lethal with offspring demonstrating defective diaphragms, skeletal defects and growth retardation. Knock-out models of inhibin, on the other hand, are born alive and at 3-4 weeks of age develop gonadal and adrenal tumors and cachexia and die shortly thereafter.

Third, as described in the de Kretser Declaration at ¶18, inhibin and follistatin compete with activin at different cellular levels such that the impact of inhibin and follistatin on activin are fundamentally different--the former being a receptor competitor and the latter being a high affinity binding protein. Importantly, inhibin may act as an activin anatagonist in some settings but not in others, whereas follistatin invariably antagonizes and blocks activin actions. Also, as noted by Dr. de Kretser at ¶19, the only noted effect of inhibin when given *in vivo* and exogenously is to inhibit the reproductive hormone, follicle-stimulating hormone; there is no

information in the public domain illustrating that inhibin can be administered *in vivo* to effectively modulate inflammatory processes.

In addition, Applicants submit that the teachings of the '862 publication are confusing and have not been substantiated by research in the years since the filing of the application that led to the '862 publication. As Dr. de Kretser points out at ¶20, statements in the '862 publication have been refuted insofar as it discloses that activin is suitable for inhibiting transplantation rejection responses. The utility of activins for inhibiting transplantation rejection is not supported by the literature, which instead teaches that an activin antagonist—follistatin—actually is beneficial in transplantation responses.

Additionally, as stated in the de Kretser Declaration at ¶22, one skilled in the art would be aware that results in an embryonic fibroblast cell line as described in the '862 publication may have limited applicability to other fibrogenic processes, and an *in vitro* result in an embryonic fibroblast lineage cannot be assumed to translate to fibrogenic processes in postnatal life; thus, the teaching is of limited or no value with regard to *in vivo* therapeutic uses of inhibin—much less follistatin—in postnatal animals. Dr. de Kretser also notes at ¶23 that inhibin fails to block the proliferative actions of activin A on 3T3 cell proliferation; yet follistatin blocks virtually all known actions of activin A. Dr. de Kretser notes further that very little can be concluded about the processes of fibrosis and tissue proliferation *in vitro* using a single cell type.

Thus, Applicants assert that the standard from *KSR* that it is obvious to substitute a known element for another to yield a known result does not apply in the context of inhibin and follistatin, and respectfully request that the rejection of the claims under 35 U.S.C. §103(a) as allegedly being unpatentable over the '862 publication be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the subject application--with pending claims 1, 2, 10, 18, 19, 30, 61, 65 and 68-78--is in condition for allowance, which action is earnestly solicited. Should the Examiner have any questions, please contact the undersigned at any time at the phone number listed below.

Respectfully submitted,

/Sarah Brashears/

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Dated: July 8, 2011

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